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#62

Docket No.: PF-0532-2 DIV

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1644

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By: D. Ellis Printed: D. Ellis

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Hillman et al.

Title:	DELTA-1-PYRROLINE-5-CARBOXYLATE REDUCTASE HOMOLOG		
Serial No.:	09/912,717	Filing Date:	July 24, 2001
Examiner:	Huynh, P.	Group Art Unit:	1644

Box AF
Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed on December 17, 2002 and received by the USPTO on December 23, 2002, herewith are three copies of Appellants' Brief on Appeal. Appellants hereby request a one-month extension of time in order to file this brief. Authorized fees include the statutory fee of **$110.00** for a one-month extension of time, as well as the $ **320.00** fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 45-47, 49, 50, 52 and 54-61 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Corporation.) (Reel 9572, Frame 0426), which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 45-47, 49, 50, 52 and 54-61
Claims allowed:	(none)
Claims canceled:	Claims 1-44
Claims withdrawn:	Claims 48, 51, 53, 62 and 63
Claims on Appeal:	Claims 45-47, 49, 50, 52 and 54-61 (A copy of the claims on appeal can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

There are no amendments after final.

(5) SUMMARY OF THE INVENTION

Embodiments of Appellants' invention are directed to an isolated antibody which specifically binds to a polypeptide ("P5CRH") having homology to delta 1-pyrroline-5-carboxylate reductase (P5CRH); i.e., an antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1. Additional embodiments of the invention provide an isolated antibody which specifically binds to a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity. (See the Specification at page 2, lines 24-36; page 3, lines 24-26 and page 43, Example X)

The antibodies of the invention can be used, for example, for the diagnosis, prevention and treatment of neuronal, connective tissue disorders and disorders of cell proliferation (see the Specification at page 3, lines 24-26; page 6, lines 26-29; page 22, lines 9-13; page 23, lines 9-13; page 23, line 35 to page 24, line 3 and page 30, lines 17-24).

(6) THE FINAL REJECTIONS

Claims 45-47, 49, 50, 52 and 54-61 stand rejected under 35 U.S.C. §112, first paragraph, based on the allegation that the claims are not supported by an enabled. The Examiner has specifically stated that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims." (September 30, 2002 Final Office Action, at page 6). The Examiner further states "[t]he specification does not teach how to make and use *any* antibody that binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1" (September 30, 2002 Final Office Action, at page 6).

Claims 45-47, 49, 50, 52 and 54-61 also stand rejected under 35 U.S.C. §112, first paragraph, based on the allegation that the claims contain "subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventor, at the time the application was filed, had possession of the claimed invention" (September 30, 2002 Final Office Action, at page 8). This rejection alleges in particular that "there is insufficient written description about the structure associated with function of an isolated antibody that binds to *any* polypeptide 'naturally-occurring' amino acid sequence at least '90% sequence identity'(sic) to the amino acid sequence of SEQ ID NO:1 for in vivo treatment of any disease and diagnostic assays."(September 30, 2002 Final Office Action, at page 10)

(7) ISSUES

1. Whether claims 45-47, 49, 50, 52 and 54-61 meet the enablement requirement of 35 U.S.C. §112 first paragraph.

2. Whether claims 45-47, 49, 50, 52 and 54-61 meet the written description requirement of 35 U.S.C. §112 first paragraph.

(8) GROUPING OF THE CLAIMS

As to Issue 1

Claims 45, 47, 49, 50, 52, 60 and 61 should be considered separately from claims 46 and 54-59.

As to Issue 2

Claims 45, 47, 49, 50, 52, 60 and 61 should be considered separately from claims 46 and 54-59.

(9) APPELLANTS' ARGUMENTS

Issue 1-Enablement rejection

Claims 45-47, 49, 50, 52 and 54-61 were rejected under 35 U.S.C. §112, first paragraph, because the Specification allegedly does not provide an enabling disclosure commensurate in scope with the claims. In particular, the Examiner has asserted that the Specification does not describe how to make and use antibodies which specifically bind to "variants" of SEQ ID NO:1. Such, however, is not the case.

At the outset, note that this rejection should not apply to claims 46 and 54-59. That is, the Examiner's position is that the Specification does not provide an adequate written description of the antibodies which specifically bind to "variants" of SEQ ID NO:1. However, claim 46 recites an antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1. Claims 54-56 and 57-59 are directed compositions and methods of making monoclonal and polyclonal antibodies, respectively, which specifically bind to a polypeptide having the amino acid sequence of SEQ ID NO:1. Accordingly, claims 46 and 54-59 should not be included with this rejection since they do not encompass the "variant" subject matter.

The Specification provides extensive detail on how to make and use the claimed antibodies. In fact, the Specification discloses methods to make antibodies which specifically bind to a polypeptide having **any** particular amino acid sequence (e.g., at page 24, line 14 to page 25, line 29; page 30, lines 17-24 and page 44, lines 13-28). Further, the Specification specifically describes variants to the amino acid sequence of SEQ ID NO:1, including variants at least 90% identical to the amino acid sequence of SEQ ID NO:1 having 1-pyrroline-5-carboxylate reductase activity (see the Specification at page 2, lines 30-36, page 5, lines 21-24; and page 12, lines 33-36). Note that claim 45 recites, *inter alia*, an antibody which specifically binds to a polypeptide comprising "***a naturally occurring amino acid sequence*** at least 90% identical to

the amino acid sequence of SEQ ID NO:1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequences of P5CRH) and SEQ ID NO:2 (the polynucleotide sequence encoding P5CRH), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. For example:

> As used herein, the term "stringent conditions" refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent, e.g., formamide, temperature, and other conditions well known in the art. In particular, stringency can be increased by reducing the concentration of sslt, increasing the concentration of formamide, or raising the hybridization temperature. (Specification at page 11, lines 2-6)
>
> In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding P5CRH or closely related molecules may be used to identify nucleic acid sequences which encode P5CRH. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low) will determine whether the probe identifies only naturally occurring sequences encoding P5CRH, allelic variants, or related sequences. (Specification at page 31, lines 3-9)
>
> Probes may also be used for the detection of related sequences, and should preferably contain at least 50% sequence identity to any of the P5CRH encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:2 or from genomic sequences including promoters, enhancers, and introns of the P56CRH gene. (Specification at page 31, lines 10-13)
>
> See also Example VI at page 41.

Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:1. Instead, one skilled in the art need only

screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. By adjusting the nature of the probe or nucleic acid (*i.e.*, non-conserved, conserved or highly conserved) and the conditions of hybridization (maximum, high, intermediate or low stringency), one can obtain variant polynucleotides of SEQ ID NO:2 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:1 recited by the present claims. Conventional methods for making antibodies, such as those described at pages 24-25 of the Specification, could be used to make antibodies which specifically bind to the recited polypeptide variants.

Moreover, Appellants submit that the invention contemplates a number of uses for antibodies which bind amino acid sequences that are variants of SEQ ID NO: 1. For example, the skilled artisan could use different antibodies to purify protein having an 1) amino acid sequence that is a variant sequence of SEQ ID NO: 1 (see Example XIII of the Specification at page 44, lines 29-36). In another use, antibodies to variants of the amino acid sequence of SEQ ID NO: 1 can be used for drug screening purposes (see the Specification at page 34 lines 30-36 and page 35 lines 1-5). Additionally, antibodies which specifically bind to variants of SEQ ID NO: 1 can be used, for example, in 2D-Page analysis for expression profiling related to toxicology testing, drug discovery and disease diagnosis. Thus, based on the multiple uses contemplated in the Specification, Appellants submit that the skilled artisan would readily know how to use antibodies to a variant of the sequence of SEQ ID NO: 1.

In regard to its specific assertions, the rejection is improper in a number of important respects. For example, in regard to the claimed naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, the Final Office Action has contended that "there is insufficient guidance and working example as [to] how the sequence can be 90% identical, much less having 1-pyrroline-5-carboxylate reductase activity." (9/30/02 Final Office Action, at page 6) This contention is untenable by virtue of the fact that the Specification provides a complete sequence listing of the amino acid sequence of SEQ ID NO::1 (see Figures 1A-1E of the Specification) as well as disclosing variants to that sequence, including variants at least 90% identical to SEQ ID NO:1 (see the Specification at page 2, lines 30-36; and page 12, lines 33-36). Given this information, Appellants submit that it is readily apparent to the skilled practitioner as to how an amino acid sequence can be 90% identical to the amino acid sequence

of SEQ ID NO:1. Appellants also submit that, given the disclosure in the Specification for assays for P5CRH activity (see the Specification at, e.g., page 43, line 7 to page 44 line 10), the skilled artisan would be able to readily identify a sequence having 1-pyrroline-5-carboxylate reductase activity.

The Office Action attempts to support the above position by citing Kuby et al. (Kuby et al: Immunology, Second edition, W.H. Freeman and Company, New York, NY, page 94, 1994.) and further postulating that "Immunization with a single peptide fragment derived from a full-length polypeptide may result in antibody specificity that differs from the antibody specificity directed against the full-length polypeptide (9/30/02, Final Office Action, at page 7). However, the Examiner missapplies this reference, because there is no requirement that the claimed antibodies have the same specificity as the antibody that binds to the full length polypeptide comprising SEQ ID NO:1. Also, even if there were such a requirement, which there is not, the Examiner provides no evidence for differing antibody specificity resulting from a single amino acid substitution of the claimed antibodies. The Court of Appeals for the Federal Circuit has recently stated that the "fact that even a single nucleotide or amino acid substitution may drastically alter the function of a gene or protein is not evidence of anything at all." (see Boehringer Ingelheim Vetmedica Inc. v. Schering-Plough Corp., No. 02-1026-1027 Fed. Cir. February 21, 2003, emphasis added)

The rejection is also in error to the extent that it relies on the Examiner's position that the "specification fails to provide any in vivo working examples" (9/30/02 Final Office Action, at page 7). There is simply no such requirement in the law. Moreover, on the subject of working examples, the M.P.E.P. states that "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." (M.P.E.P. section 2164.02)".

The rejection is further flawed with respect to the contention in the Final Office Action concerning chimeric antibodies. Specifically the Examiner stated that:

> "In the absence of in vivo working examples, it is (sic) unpredictable for the following reasons: (1) the antibody may be inactivated before producing an effect, i.e. such as inherently short half-life of the antibody; (2) the antibody may not reach the target area; and (3) other function properties, known or unknown, may make the antibody unsuitable for *in vivo* therapeutic use" (9/30/02 Final Office Action, at page 7).

In support of this assertion the Examiner cites the '370 patent, which according to the Examiner, "teaches that the inherent problem with chimeric antibody (sic) has been a loss of affinity, which means more antibody will have to be injected into a patient at higher cost and greater risk of adverse effects (see column 2 lines 12-27, in particular)" (9/30/02 Final Office Action, at page 7). No where in the law is patentability precluded by either the cost or potential adverse effects (e.g., safety) of an invention. In fact, in regard to safety as a requirement for enablement, the M.P.E.P. specifically states that "[t]he applicant need not demonstrate that the invention is completely safe." (M.P.E.P. section 2164.01(c)).

The rejection is also untenable because the claimed chimeric antibodies are not limited to a recited use, e.g., human use. In this regard, the M.P.E.P. states the following:

> In contrast, when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention. (M.P.E.P. 2164.02 (c), emphasis added)

In addition to the human uses, the recited chimeric antibodies can be used, for example, to detect and/or purify polypeptides which are specifically bound by the recited antibodies (See Example XIII of the Specification at page 44, lines 29-36). Thus even if *in arguendo,* the claimed antibodies were not enabled for human use (which is expressly not the case) the fact that the recited chimeric antibodies can be used for in vitro applications whose enablement is undisputed, renders the claimed chimeric antibodies enabled. Further, because the Examiner has not provided any explanation, let alone an explanation "supported by the evidence" as to why these other disclosed uses are not enabled, the rejection is critically flawed. Therefore, it would not require undue experimentation of one skilled in the art to use the antibodies of the claimed invention.

Moreover by rejecting the claimed chimeric antibodies for allegedly having "higher cost" and a "greater risk of adverse effect" the Examiner appears to be premising the rejection on a

requirement that the claimed antibodies must be optimal. However, no such requirement exists in the law. In fact, in *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.* the court held that in regard to enablement, optimality is not required for a valid patent. (see *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 750 F.2d 1569, 1580, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984)).

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 ***requires nothing more than objective enablement***. [emphasis added] How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited antibodies which specifically bind to the recited "variants" of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established with respect to the claimed antibodies which specifically bind to the recited "variants" of SEQ ID NO:1.

For at least the above reasons, reversal of this rejection is requested.

Issue 2 Written description rejection

The rejection of claims 45-47, 49, 50, 52 and 54-61 is in error; the claims meet the written description requirement of 35 U.S.C. 112, first paragraph.

Claims 45-47, 49, 50, 52 and 54-61 have been rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. In particular, the rejection appears to be based on the statement in the Final Office Action that "there is insufficient written description about the structure associated with function of an isolated antibody that binds to *any* polypeptide 'naturally-occurring' amino acid sequence at least '90% sequence identity'(sic) to the amino acid sequence of SEQ ID NO:1 for in vivo treatment of any disease and diagnostic assays (sic)" (9/30/02 Final Office Action, at page 11). This rejection is improper, as the claims define subject matter which is described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed subject matter at the time the application was filed.

At the outset, note that this rejection should not apply to claims 46 and 54-59. That is, the Examiner's position is that the Specification does not provide an adequate written description of the antibodies which specifically bind to "variants" of SEQ ID NO:1. However, claim 46 recites an antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1. Claims 54-56 and 57-59 are directed compositions and methods of making monoclonal and polyclonal antibodies, respectively, which specifically bind to a polypeptide having the amino acid sequence of SEQ ID NO:1. Accordingly, claims 46 and 54-59 should not be included with this rejection since they do not encompass the "variant" subject matter.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q2d 1111, 1117 (Fed. Cir. 1991).

The Boards Attention is also drawn to the Patent and Trademark Office's own

"Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1," published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46] [Footnotes omitted]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The Specification provides an adequate written description of the claimed antibodies which specifically bind to the recited "variants" of SEQ ID NO:1.

The subject matter encompassed by claims 45-47, 49, 50, 52 and 54-61 is either disclosed by the Specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 45 recites polypeptides "comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity." The polypeptide sequence of SEQ ID NO:1 is explicitly disclosed in the Specification (see, e.g. the Sequence Listing and Figures 1A, 1B, 1C, 1D and 2 of the Specification). Variants of SEQ ID NO:1 are described in the Specification at, for example, page 2, lines 30-36; page 5, lines 21-24; and page 12 lines 33-39. In addition, a specific assay to measure P5CRH activity is disclosed in the Specification at, for example, page 43, line 7 to page 44 line 10. The Specification also describes the production of antibodies to P5CRH proteins at, for example, page 6, lines 32 to page 7, line 1.

Appellants submit that one of ordinary skill in the art would recognize polypeptide sequences which are variants that are at least 90% identical to SEQ ID NO:1. Given any naturally occurring polypeptide sequence, it would be routine for one of skill in the art to

recognize whether it was a variant of SEQ ID NO:1. It would also be routine to determine whether such a variant had P5CRH activity, using the disclosed P5CRH assay. Accordingly, the Specification provides an adequate written description of the claimed antibodies which specifically bind to the recited polypeptide variants of SEQ ID NO:1.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 U.S.P.Q2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 U.S.P.Q2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 U.S.P.Q2d at 1603, the parties were in an interference involving the

following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define the polypeptides bound by the claimed antibodies in terms of chemical structure, rather than functional characteristics. For example, the language of independent claim 45 recites chemical structure to define the claimed genus:

> 45. An isolated antibody which specifically binds to a polypeptide selected from the group consisting of:
> a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, and
> b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides specifically bound by the claimed antibodies. The polypeptides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims

of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant". Available evidence illustrates that, rather than being a large variable genus, the genus of polypeptides recited by the claims is of narrow scope.

In support of this assertion, the Board's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to polypeptides which are delta 1-pyrroline-5-carboxylate reductases, including polypeptides which are delta 1-pyrroline-5-carboxylate reductases related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as delta 1-pyrroline-5-carboxylate reductases and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites a polypeptide comprising "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 314 amino acid residues). This variation is far less than that of all potential delta 1-pyrroline-5-carboxylate reductases related to SEQ ID NO:1, i.e., those short-chain dehydrogenases having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of June 18, 1998. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed antibodies which specifically bind the recited polypeptide variants at the time of filing of this application.

4. Summary

The Final Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Office Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims reciting nucleic acids and proteins. In addition, the genus of polypeptides recited by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there

have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the Specification provides an adequate written description of the claimed antibodies which specifically bind to the recited polypeptide "variants". Accordingly, Appellants respectfully submit that the rejection should be reversed.

(10) CONCLUSION

Appellants respectfully submit that the enablement and written description rejections are without merit. The rejections are, therefore, improper and should be reversed.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. 09-0108.

This brief is enclosed in triplicate

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: 24 March 2003

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APPENDIX - CLAIMS ON APPEAL

45. An isolated antibody which specifically binds to a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, and

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity.

46. The antibody of claim 45 which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1.

47. The antibody of claim 45 which specifically binds to a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity.

49. The antibody of claim 45, wherein the antibody is:

a) a chimeric antibody,

b) a single chain antibody,

c) a Fab fragment,

d) a $F(ab')_2$ fragment, or

e) a humanized antibody.

50. A composition comprising an antibody of claim 45 and an acceptable excipient.

52. A composition of claim 50, wherein the antibody is labeled.

54. A method of preparing a polyclonal antibody with the specificity of the antibody of claim 45, the method comprising:

a) immunizing an animal with a polypeptide having the amino acid sequence of SEQ ID NO:1, or an immunogenic fragment thereof, under conditions to elicit an antibody response,

b) isolating antibodies from said animal, and

c) screening the isolated antibodies with the polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having the amino acid sequence of SEQ ID NO:1.

55. A polyclonal antibody produced by a method of claim 54.

56. A composition comprising the polyclonal antibody of claim 55 and a suitable carrier.

57. A method of making a monoclonal antibody with the specificity of the antibody of claim 45, the method comprising:

a) immunizing an animal with a polypeptide having the amino acid sequence of SEQ ID NO:1, or an immunogenic fragment thereof, under conditions to elicit an antibody response,

b) isolating antibody producing cells from the animal,

c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells,

d) culturing the hybridoma cells, and

e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide having the amino acid sequence of SEQ ID NO:1.

58. A monoclonal antibody produced by a method of claim 57.

59. A composition comprising the monoclonal antibody of claim 58 and a suitable carrier.

60. The antibody of claim 45, wherein the antibody is produced by screening a Fab expression library.

61. The antibody of claim 45, wherein the antibody is produced by screening a recombinant immunoglobulin library.